REMARKS/ARGUMENTS

Status of the claims

With entry of the instant amendment, claims 127, 128, 132, 137, and 148 are amended. Claims 127, 128, and 148 are amended to recite that the compositions comprises two single-copy probes that have a combined length of at least 50 kb. Support can be found, *e.g.*, at page 22, last full paragraph of the specification as filed, which teaches that the size distribution of the nucleic acid probes can be adjusted; at page 37, lines 4-7 of the specification as filed, which provides examples of probe sizes; and on page 41, lines 23-24, which teaches that a single-copy probe binds to a single-copy target sequence. Support for the amendments to claims 127, 128 and 148 with respect to recitation of "a region of the ABL gene telomeric to the 200 kb region between exons Ib and II" and "a region of the BCR gene centromeric to the breakpoint region" can be found, *e.g.*, at the second paragraph on page 30 and at the third paragraph on page 115 of the specification as filed. Support for the amendment to claim 128 to recite more specific probe sizes of at least 35 kb with respect to the probe that hybridizes to a part of the ABL gene and at least 18 kb with respect to the probe that hybridizes to a part of the BCR gene can be found, *e.g.*, at page 115, second and third paragraphs, and Figure 8. Support for the amendments to claims 132 and 137 are found, *e.g.*, in the claims as filed.

Cancellation of subject matter by amendment is without prejudice to revival for prosecution in this application or an application claiming priority to this application.

Claims 127, 128, 130-134, 136-142, and 146-155 are pending and under examination.

Applicants thank the Examiner and Supervising Examiner for the interview on August 3, 2011 with the undersigned and Richard Lazarus, additional counsel for co-assignee the University of Chicago, during which the rejections and potential amendments were discussed. The amendments to the claims add specific structural characteristics of the BCR and ABL probes and, with respect to claim 132, recite that the probes are hybridized to chromosomal DNA *in situ* in the cells, as discussed during the interview.

Drawings

Applicants are in the process of trying to obtain the required three sets of color drawings and will file the necessary copies and petition along with the amendment to the specification to insert the required statement; or will amend the application as proposed by the Examiner.

Claim objection

Applicants thank the Examiner for noting the typographical error in claim 137. This has been corrected by the amendment to claim 137.

Rejections under 35 U.S.C. § 103

Claims 127, 128, 130-134, 136, 139-141, 148, and 149 are rejected as allegedly obvious over Bartram *et al.*, *The EMBO J.* 4:683-686, 1985 ("Bartram") over Hopman *et al.*, *Histochemistry* 85:1-4, 1986 ("Hopman") in view of Hariharan *et al.*, *The EMBO J.* 6:115-119, 1987 ("Hariharan"), in view of Shtivelman *et al.*, *Cell* 47:277-284, 1986 ("Shtivelman") in view of Lawrence e*t al.*, *Cell* 52:51-61, 1988 ("Lawrence"). Applicants have traversed this rejection for reasons of record. In the interests of expediting prosecution, however, claims 127, 128, and 148 are amended as explained above. To the extent that the Examiner may believe that the rejection applies to the amended claims, Applicants respectfully traverse.

The current claims recite two single copy probes, each labeled with distinguishable label, for detecting a chromosomal aberration involving the BCR and ABL genes where probes are characterized by a certain size (they have a combined length of at least 50 kb); and by where they bind (the ABL gene probe hybridizes to the ABL gene telomeric to the 200 kb region between exons Ib and II and the BCR probe hybridizes to the BCR gene centromeric to the breakpoint region. The probes set forth in the claims thus have defined structural properties. The combination of references cited in the rejection does not teach or suggest such a probe composition.

As previously explained, Bartram employs radioactively labeled probes for *in situ* hybridization for the analysis of a translocation in a Philadelphia chromosome-negative patient.

However, the combined sizes of Bartram's probes appear to be much less than the probe size recited in the claims. (See, *e.g.* Bartram, methodology on page 686, lines 7-11, first column; the size of the BCR sequences indicated in Figure 3 is not apparent from Bartram's disclosure). Moreover, Bartram required statistical analysis of the number of silver grains distributed over the chromosomes to determine to which metaphase bands the probes were hybridizing. Bertram provides no suggestion that two different distinguishable labels could be employed at the same time such that it could be reliably determined which probe is binding to what site.

Hopman employs two probes, each labeled with a distinguishable label; however, the target sequences were highly repeated (see, *e.g.*, page 3 of Hopman). Hopman states that middle and low repeated sequences are within the sensitivity of his techniques (Hopman, p. 3), but provides no teaching or suggestion that his technique would be sufficiently sensitive to use two probes together having the structural properties recited in the claims where the probes are single copy probes and each probe detects a unique sequence.

Lawrence is characterized in the rejection as purportedly teaching that use of a fluorescent-labeled probe to detect a single copy sequence is possible. This is not the same as demonstrating success using the methods claimed here. The Examiner characterizes Lawrence as teaching that the viral genes are integrated into human chromosomes and that Lawrence detects the integrated viral genes using a single copy viral probe that is fluorescently labeled. According to the Examiner's analysis, Lawrence therefore supports the position that it is possible to detect a single copy gene sequence. Applicants respectfully disagree with the Examiner's analysis of Lawrence's disclosure for reasons of record. Lawrence used a known, specific virus integrated into a known site on a single chromosome as the target and used a specialized cancer cell line harboring the integrated viral sequence. This is a very different system that that employed by the inventors here, which uses probes as defined in the claims to detect chromosomal aberrations. In the response filed March 3, 2011, Applicants pointed out a passage in Lawrence at page 58, 2nd column, which ndicated that the results (Lawrence's results)must take into consideration the possibility that the integrated viral genome exhibits less condensation than the rest of the chromosomal DNA. Although the Examiner contends that that this is related to the effect of the extent of condensation on the distance between two copies of viral inserts in

the chromosome (Section 12, of May 5, 2011 Office Action), the statement nonetheless points to differences in detecting integrated viral genomes in comparison to detecting chromosomal aberrations. Even though Lawrence was able to detect viral sequences in both interphase and metaphase chromosomes, this does not mean that two probes one for the BCR gene and one for the ABL gene, could be employed that would allow for the detection of chromosomal aberrations involving BCR and ABL. Furthermore, Lawrence provides no teaching or suggestion as to the features of the probes encompassed by the amended claims, *e.g.*, the combined lengths, where on the BCR and ABL genes such probes would bind, that would be appropriate for an in-depth cytogenetic analysis required for evaluating a chromosomal aberration involving BCR and ABL.

The totality of the teachings of Bertram, Hopman, and Lawrence thus do not lead one of skill in the art to reasonably expect that the technique of Bertram could successfully be modified to employ two probes, each labeled with a different label, to detect two unique sequences in a chromosomal aberration involving BCR and ABL. Although Hariharan and Shtivelman are cited as allegedly teaching probes for BCR and ABL, respectively, neither reference provides any evidence of the types of probes that would be suitable for a composition comprising two probes that together identify chromosomal aberrations involving BCR and ABL.

The Supreme Court has "warn[ed] against 'temptation to read into the prior art the teachings of the invention in issue' and instruct[ed] courts to 'guard against slipping into the use of hindsight.'" *KSR Int'l v. Teleflex Inc.*, 127 S.Ct 1742 (2007), quoting *Graham v. John Deere Co.*, 383 U.S. 1 (1966) at 36. Here, it is only Applicants' disclosure that provides the basis for developing a combination of probes as recited in the current claims. The rejection is thus improper, as it reads into the prior art the teaching of the invention at issue.

The following rejections were also maintained:

The rejection of claims 127, 132-134, 136-138, 146, and 147 over Bartram, Hopman, Hariharan, Shtivelman and Lawrence in view of Ribeiro *et al., Blood* 70:948-953, 1987 ("Ribeiro");

The rejection of claims 127, 132, and 142 over Bartram, Hopman, Hariharan, Shtivelman, and Lawrence in view of Selden *et al., Proc. Natl. Acad. Sci USA* 80:7289-7292, 1983 ("Selden");

The rejection of claims 127, 128, 148, 151, 152, and 154 over Bartram, Hopman, Harkharan, Shtivelman and Lawrence in view of Lau *et al., Proc. Natl. Acad. Sci* USA 80:5225-5229, 1983 ("Lau") as evidenced by Westbrook, U.S. Patent No. 6,575,421; and

The rejection of claims 127, 128, 148, 150, 153, and 155 as allegedly obvious over Bartram, Hopman, Harkharan, Shtivelman and Lawrence in view of Frischauf *et al., J. Mol. Biol* 170:827-842, 1983 ("Frischauf") as evidenced by Westbrook, U.S. Patent No. 6,575,421.

As Applicants have previously noted, the teachings of the secondary references cited in these rejections do not compensate for the deficiencies of the primary references. None of the secondary references provide specific teachings as to the structure of probes that can be each labeled with a distinguishable label and employed in a composition to detect chromosome aberrations involving BCR and ABL. Accordingly, the claims at issue in each of the rejections are unobvious over the combinations of primary and secondary references for the reasons described above with respect to the rejection of claims 127, 128, 130-134, 136, 139-141, 148, and 149 over the combination of Bartram, Hopman, Harkharan, Shtivelman and Lawrence.

In view of the foregoing, the claimed invention is patentable over the cited art. Applicants respectfully request that all of the rejections under 35 U.S.C. § 103 be withdrawn.

Obviousness-type double patenting rejections

Claims 127, 128, 130, 131, and 148 are rejected for alleged obviousness-type double patenting over claims 3 and 11 of U.S. Patent No. 6,280,929 (the '929 patent). Claim 137 is rejected for alleged obviousness-type double patenting as unpatentable over claims 3 and 11 of the '929 patent in view of Bertram in view of Ribiero. Applicants respectfully disagree with the rejection for reasons as stated in the amendment filed March 3, 2011.

Claims 127, 128, 130-134, 136-142, 146-148, and 150-155 are rejected as allegedly unpatentable over claims 3, 7, 8, 10-16, 19, 21, 22, 24, and 26-36 of U.S. Patent No. 6,576,421 (the '421 patent). Applicants respectfully disagree with the rejection for reasons as stated in the amendment filed March 3, 2011. As previously explained, the obviousness-type double patenting rejections applied here are inconsistent with longstanding USPTO policy that methods are patentably distinct inventions relative to compositions. The compositions claimed

in the present application are patentably distinct from the method claims of the '929 and '421 patents.

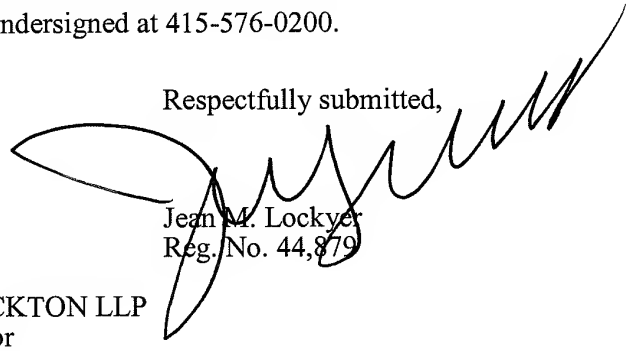
Further, with regard to the '421 patent, a composition employing two probes is unobvious over the methods employing three probes. Moreover, the second requirement for obviousness-type double patenting in the MPEP, that "issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent" does not apply to the '421 patent claims that require three probes. That method patent did not depend on patentability of the two probes claimed at present, and patenting claims that can employ two probes does not result in unjustified extension of the term of the patent for methods that require three probes.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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